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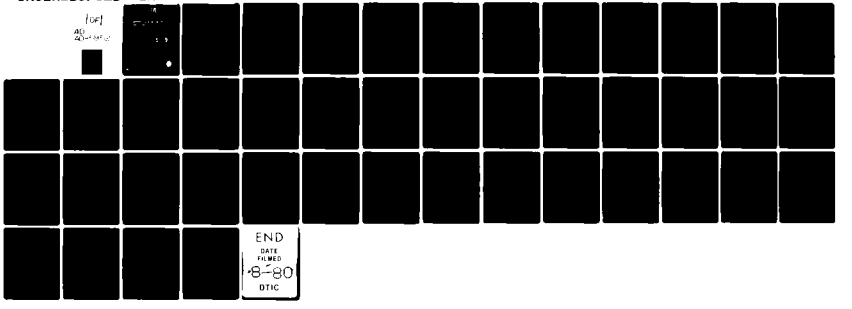

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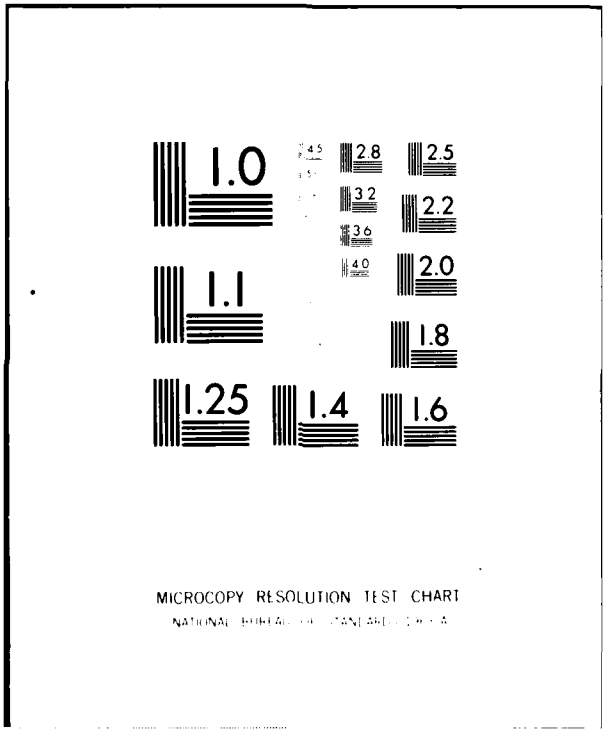
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RADIOFREQUENCY RADIATION AND LIVING TISSUE: THEORETICAL STUDIES

Richard A. Albanese, M.D.
Earl L. Bell, M.S.

December 1979

Interim Report for Period January 1978 - May 1979

Approved for public release; distribution unlimited.

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
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This interim report was submitted by personnel of the Biomathematics Modeling Branch, Data Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 7757-01-69.

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This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

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Basic mechanisms whereby radiofrequency electromagnetic radiation can interact with living tissue were investigated. An elementary statistical physics model of tissue, viewed as a chemical mixture, was considered, followed by a nonquantum physics analysis of macromolecular motion in an electromagnetic field. These studies of basic mechanisms suggest that radiofrequency electromagnetic radiation may be important in its effect on living tissue without causing significant tissue-temperature rises.

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RADIOFREQUENCY RADIATION AND LIVING TISSUE: THEORETICAL STUDIES

This report is concerned with basic mechanisms whereby radiofrequency electromagnetic radiation can interact with living tissue. Our analysis of basic mechanisms suggests that radiofrequency electromagnetic radiation may be significant in its effect on living tissue.

Part I of this report outlines an elementary statistical physics model of tissue viewed as a chemical system. Part II presents a nonquantum physics analysis of macromolecular motion in an electromagnetic field. The final section, Part III, provides a discussion and recommendation for further analysis and experimentation.

PART I: STATISTICAL PHYSICS MODEL OF TISSUE

THE MODEL TISSUE

The approach taken here is to model tissue as a mixture of two molecular types, #1 and #2. Type #1 is thought of as cell water, and type #2 consists of biomacromolecules. Type #1 molecules can exist in energy levels U_{11}, U_{12}, U_{13}, ..., U_{1L}; while type #2 molecules can exist in energy levels U_{21}, U_{22}, U_{23}, ..., U_{2M}. These molecules are considered to be only weakly interacting and each is considered distinguishable according to its spatial position or orientation, so that Maxwell-Boltzmann distribution theory is valid (13).

Let the symbol x_{ij} represent the number of molecules of type i in energy state U_{ij}. If the total number of molecules of type #1 is N_1, then

$$\sum_{j=1}^{L} x_{1j} = N_1 \tag{1}$$

and, if the total number of molecules of type #2 is N_2, then

$$\sum_{j=1}^{M} x_{2j} = N_2 \tag{2}$$

Each energy level U_{ij} has an associated set of g_{ij} elementary eigenstates, as schematically represented in Figure 1 (13). Therefore, for the ensemble of type #1 molecules, the total number of possible eigenstates associated with the occupancy numbers $x_{11}, \ldots, x_{1L}$ is G_1, where

$$G_1 = \frac{N_1!}{x_{11}!\ldots x_{1L}!} \; g_{11}^{x_{11}} \ldots g_{1L}^{x_{1L}} \tag{3}$$

Likewise, for the type #2 molecules, G_2 is

$$G_2 = \frac{N_2!}{x_{21}!\ldots x_{2M}!} \; g_{21}^{x_{21}} \ldots g_{2M}^{x_{2M}} \tag{4}$$

Let

$$p_{ij} = \frac{g_{ij}}{\sum_j g_{ij}} \tag{4.1}$$

This value p_{ij} can be considered as the a priori probability of the energy level U_{ij}. Substituting in the above relation, the following equations are obtained:

$$P_1 = \frac{N_1!}{x_{11}!\ldots x_{1L}!} \; p_{11}^{x_{11}} \ldots p_{1L}^{x_{1L}}$$

$$P_2 = \frac{N_2!}{x_{21}!\ldots x_{2M}!} \; p_{21}^{x_{21}} \ldots p_{2M}^{x_{2M}} \tag{4.2}$$

where P_1 and P_2 are the probabilities of the occupancy configurations $x_{11}, \ldots, x_{1L}$ and $x_{21}, \ldots, x_{2M}$, respectively. Whence the total system probability can be written as

$$P = P_1 P_2$$

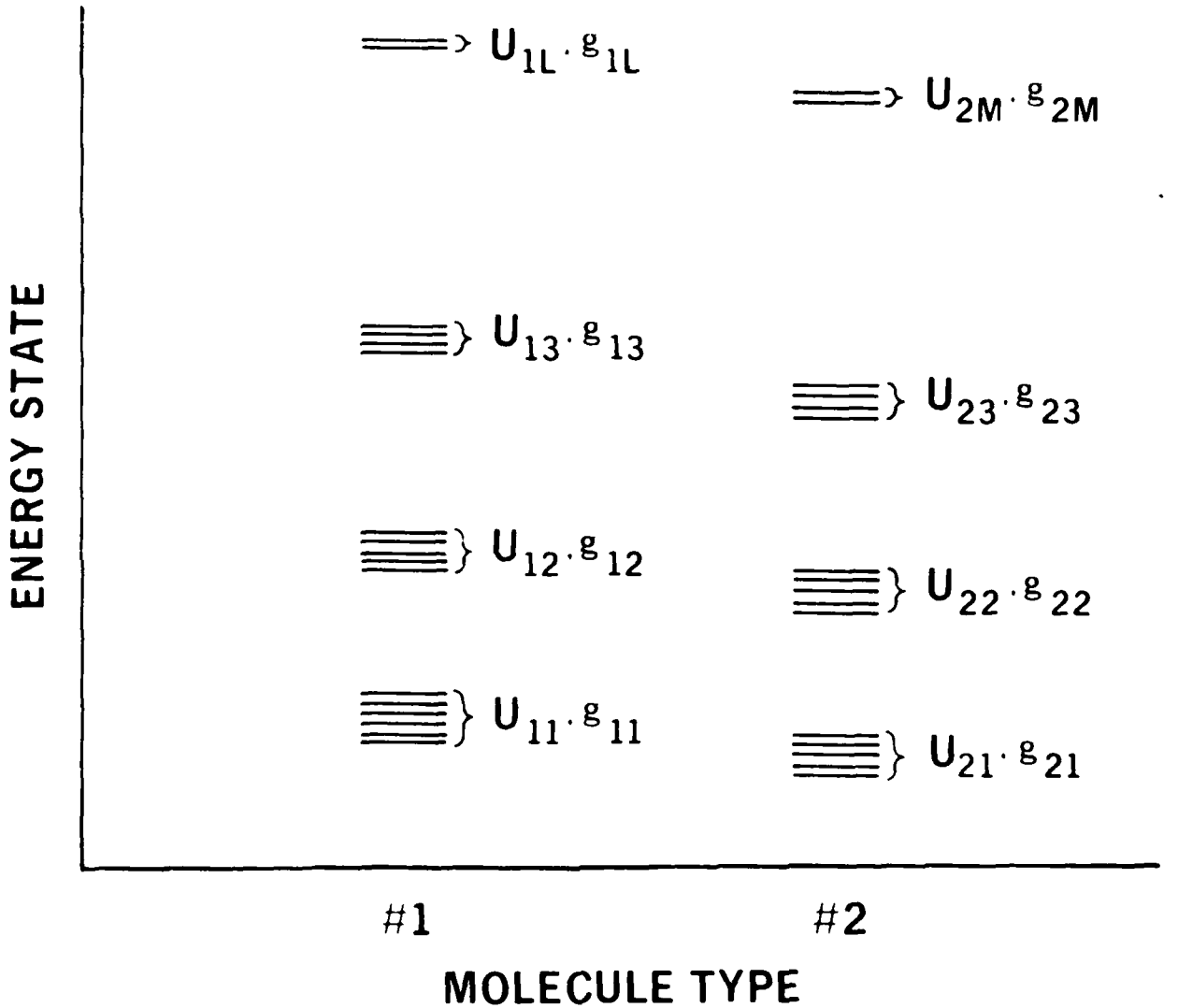

Figure 1. Energy state structure of the model tissue.

It is shown in Appendix A that, if the mixture is in a state of equilibrium, the following relationships hold for n_{1j} (the most likely value of x_{1j}) and for n_{2j} (the most likely value of x_{2j}):

$$n_{1j} = p_{1j} N_1 \exp(-U_{1j}/kT) \left\{ \sum_{r=1}^{L} p_{1r} \exp(-U_{1r}/kT) \right\}^{-1}$$

$$n_{2j} = p_{2j} N_2 \exp(-U_{2j}/kT) \left\{ \sum_{r=1}^{M} p_{2j} \exp(-U_{2r}/kT) \right\}^{-1} \quad (5)$$

In these last two equations, k is the Boltzmann constant and T is temperature given in degrees Kelvin. Note that the total system energy, U, can be calculated using the following equation:

$$\sum_{j=1}^{L} n_{1j} U_{1j} + \sum_{j=1}^{M} n_{2j} U_{2j} = U \quad (6)$$

MODEL OF RADIATION-INDUCED TRANSITIONS

For purposes of illustration, a tissue with only four energy states is considered. Type #1 molecules have energy states U_{11} and U_{12}, and type #2 molecules have energy states U_{21} and U_{22}. Since type #2 molecules represent biomacromolecules, photon-stimulated transitions between U_{21} and U_{22} are examined.

Consider first the transitions between U_{21} and U_{22} when the tissue is not receiving externally applied radiation and is in a state of equilibrium. If C_{21} is the equilibrium rate of transition from U_{21} to U_{22} per second per molecule, and C_{22} is the analogous rate for the reverse transition, equilibrium requires:

$$C_{21} n_{21} = C_{22} n_{22} \quad (7)$$

To analyze transitions due to radiation, transition probabilities are used as follows: (1) B_{21} is the probability of transition from U_{21} to U_{22} by photon absorption per molecule in U_{21} and per unit field intensity (e.g., 1 mW/cm^2);

(2) B_{22} is the probability of transition from U_{22} to U_{21} by stimulated photon emission per molecule in U_{22}, and per unit field intensity.

Considering the case wherein the added radiation does not significantly perturb mixture total energy, when the mixture achieves a new equilibrium with the radiation, the following equality must hold:

$$(B_{21}I + C_{21})(n_{21} - \Delta) = (B_{22}I + C_{22})(n_{22} + \Delta) \tag{8}$$

In this equation, n_{21} and n_{22} are the equilibrium values calculated by equations 4 and 5, Δ is the change in n_{21} and n_{22} due to the externally applied radiation, and I is the radiation exposure received from an outside source or sources. It is well known that $B_{21} = B_{22} = B$. Using this, it is found that:

$$\Delta = \frac{BI\,(n_{21} - n_{22})}{2BI + C_{21} + C_{22}} \tag{9}$$

Equations 4, 5, 6, and 9 allow exploration of radiation effects in a tissue when tissue temperature does not change significantly. A simple example is calculated in the next subsection.

A CALCULATED EXAMPLE

Suppose the tissue is described by parameters as given in Table 1. Recall that type #1 molecules represent cell water molecules while type #2 molecules represent biomacromolecules. In Table 1, the value used for N_1 is the number of water molecules in a sphere with a 10-μm radius, the sphere representing a small cell. The value for N_2 is an estimated number of enzyme molecules of a particular type in a single cell. The energy levels in the enzyme are chosen so that transitions can be caused by 500-MHz radiation. The upper enzyme mode with energy U_{22} is given a low probability, p_{22}, to achieve a mode that is poorly populated in the absence of external radiation. For example, the energy U_{22} may correspond to a first step in enzyme denaturation, which may not be favored in unirradiated tissue.

TABLE 1. TISSUE SPECIFICATIONS

U_{11} = 1.0 kT

U_{12} = 2.0 kT

U_{21} = 1.5 kT

U_{22} = 1.5 kT + $h\gamma$

γ = 500 megahertz

h = Planck's constant

P_{11} = 0.70

p_{12} = 0.30

P_{21} = 0.9999

p_{22} = 0.0001

N_1 = 1.4 x 10^{11}

N_2 = 1.0 x 10^6

T = 310°K

B = 750 transitions per second per milliwatt/cm^2 per molecule

C_{21} = 0.0375 transitions per second per molecule

In choosing the transition coefficient B, a molecule with average cross-sectional area of 2,500 square Angstroms was considered. This corresponds to a spherical molecule with radius 28.21 Angstroms. In a 1 mW/cm^2, 500-MHz field, this molecule will be struck by 750,000,000 photons per second. The coefficient B was chosen to provide one transition per million photons.

Examining equation 9, we see that in the model under discussion here, the maximum Δ achievable is $(n_{21} - n_{22})/2$. In Table 1, C_{21} is chosen so that a perturbation of approximately $\Delta/2$ is achieved at 0.25 mW/cm^2.

Using equations 4, 5, and 6, the tissue configuration prior to external irradiation can be described. Specifically, energy state occupancy and total tissue energy can be calculated. These values are shown in Table 2 for the model tissue at T = 310°K.

TABLE 2. TISSUE ENERGY-STATE OCCUPANCY AND TOTAL ENERGY WITHOUT EXTERNAL RADIATION

$n_{11} = 1.2093 \times 10^{11}$ $\qquad$ $n_{21} = 999900$

$n_{12} = 0.1907 \times 10^{11}$ $\qquad$ $n_{22} = 99.9923$

$U = 6.8069 \times 10^{-10}$ joules

$(T = 310°K)$

In Figure 2, tissue total energy is plotted as a function of temperature. In Figure 3, n_{22} is plotted as a function of temperature. Tables 3 and 4, respectively, show the data for these figures. An insignificant increase in n_{22} occurs as a function of temperature. This is due to the closeness of the energy levels U_{21} and U_{22}.

TABLE 3. TOTAL TISSUE ENERGY AS A FUNCTION OF TEMPERATURE

Temperature (°K)	Energy (joules)
310	6.8069×10^{-10}
360	6.9098×10^{-10}
410	6.9945×10^{-10}
460	7.0651×10^{-10}

TABLE 4. n_{22} AS A FUNCTION OF TEMPERATURE

Temperature (°K)	n_{22}
310	99.9923
360	99.9933
410	99.9941
460	99.9948

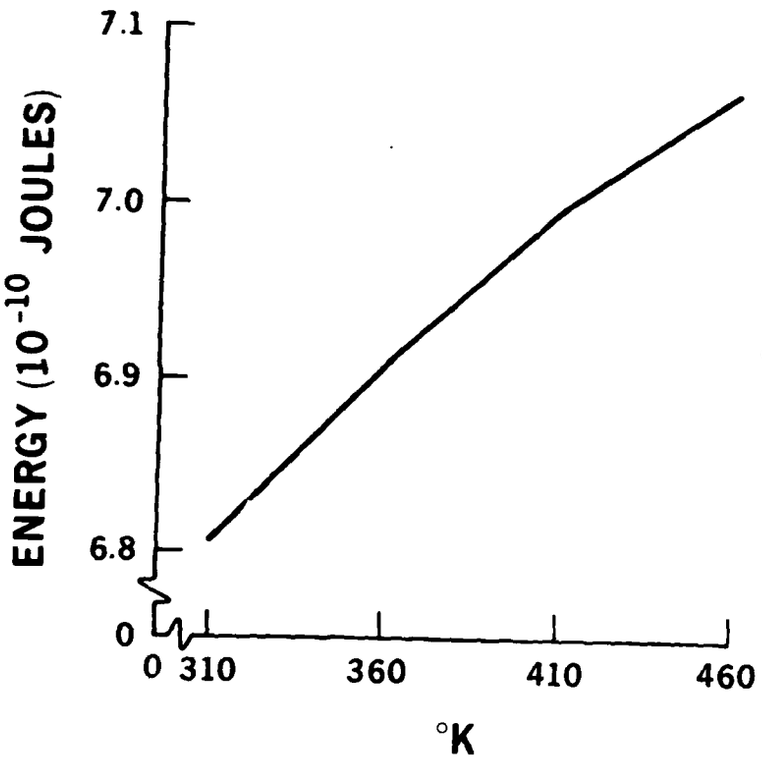

Figure 2. Tissue energy as a function of temperature.

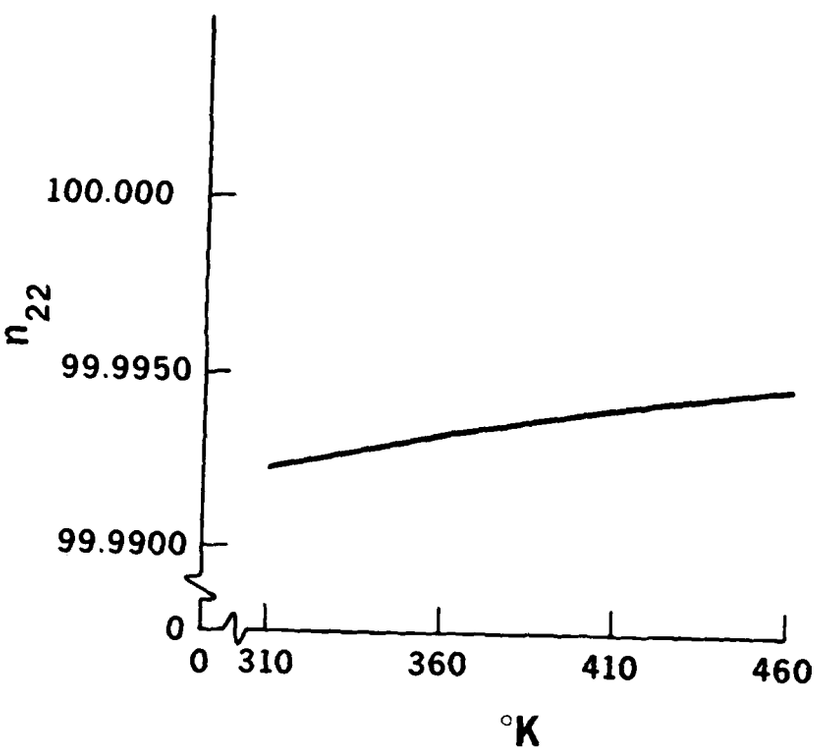

Figure 3. Biomacromolecule upper energy level occupancy as a function of temperature.

Table 5 shows the model tissue receiving 0.25 mW/cm^2 of 500-MHz radiofrequency radiation. No significant change in the "water" molecules is noted; that is, no significant change occurs in n_{11} or n_{12}. Neither is there any significant change in total system energy U, indicating essentially no tissue temperature rise. However, n_{22} is markedly pumped. Figure 4 shows n_{21} and n_{22} as functions of irradiation intensity. This figure indicates pumping at quite low dose levels; the tissue "enzyme" is effectively very "hot" even at 0.001 mW/cm^2 (recall Figure 3).

TABLE 5. MODEL TISSUE UNDER 0.25 mW/cm^2 OF 500-MHz RADIOFREQUENCY RADIATION

$n_{11} = 1.2093 \times 10^{11}$ $\qquad$ $n_{21} = 749{,}959$

$n_{12} = 0.1907 \times 10^{11}$ $\qquad$ $n_{22} = 250{,}040$

$U = 6.8069 \times 10^{-10}$ joules

$(T = 310°K)$

A small BASIC language computer program was written to calculate the data presented in Tables 2 through 5 and in Figures 2 through 4. A listing of this program is provided in Appendix B.

What is the meaning of the data presented in the above discussion? Overall, the above-outlined elementary model reinforces the point:

"IF A MOLECULAR TRANSITION IS SHIELDED FROM COLLISIONAL STIMULATION, BUT CAN BE STIMULATED BY ELECTROMAGNETIC RADIATION, THE RADIATION EFFECT CAN PUMP THE TRANSITION."

Two questions are immediate: (1) What may be the biomedical consequences of pumping a transition? (2) How can we study this phenomenon experimentally?

Changing the state of a molecule can change its chemical reactivity. The biomedical impact of pumping, then, can be expected to shift biochemical reaction rates and pathways in the living being. Considering this phenomenon from the biochemical-evolutionary point of view is worthwhile. The state or conformation of a biomacromolecule is very important to its reactivity. As a

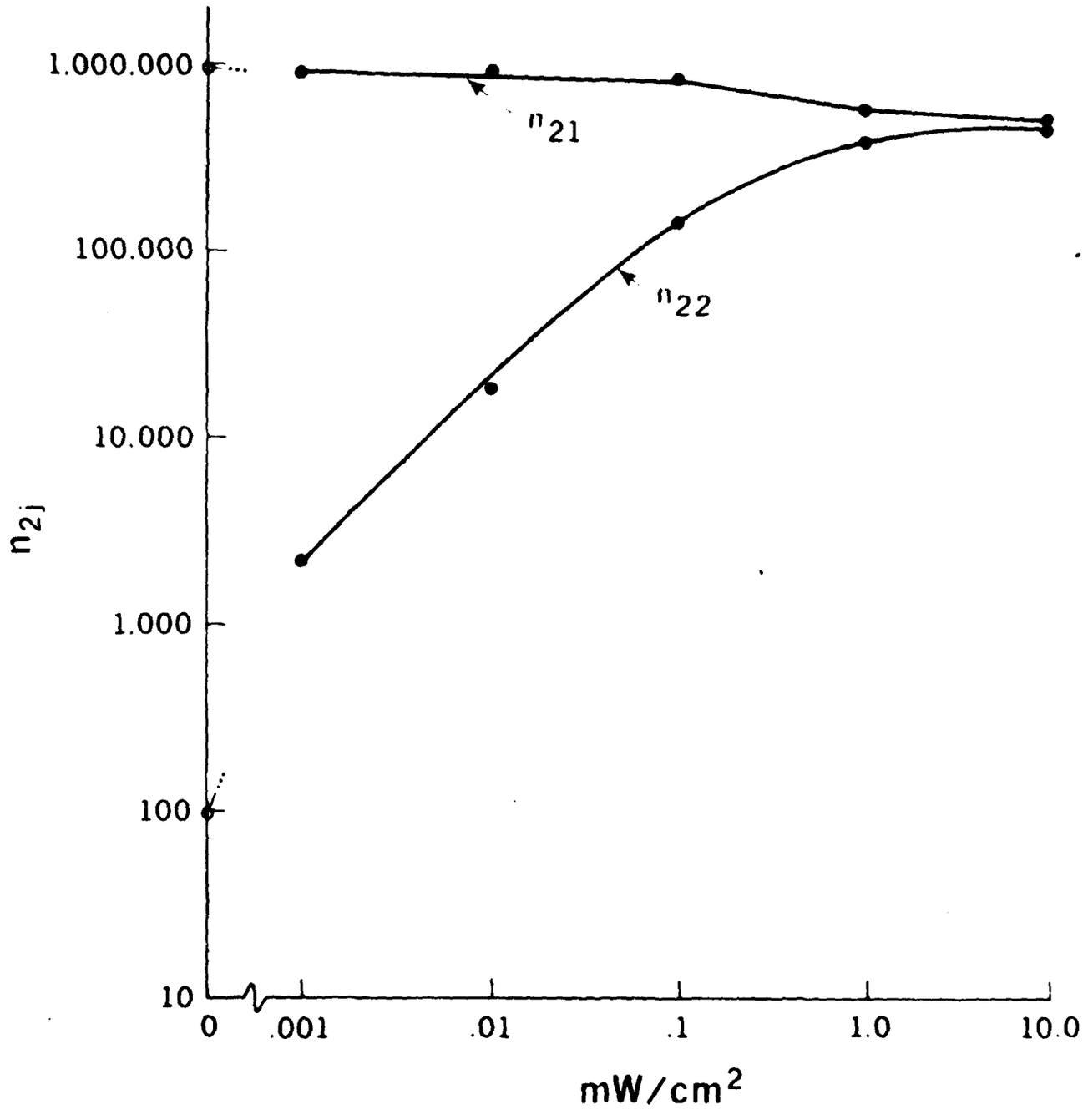

Figure 4. Biomacromolecule energy level occupancy as a function of exposure.

species evolves, key molecular conformations may be shielded from collisional transitioning to promote macromolecular stability. These conformations, then, could be vulnerable to radiofrequency radiation.

At least four research teams have investigated chemical reaction rates in electromagnetic fields. Chen et al. (1) observed a small shift in the equilibrium constant of an iron oxidation-reduction system in a high magnetic field. Wayland and Brannen (2) required an electric field term to explain their thermal inactivation curves for Bacillus subtilis. Seto and Hsieh (3) provided some very interesting theory and experimental work with Escherichia coli, while Karube et al. (4) had an intriguing result with membrane-bound lipase.

From the medical point of view, changes in chemical reaction rate might particularly be detected in clinical measures such as tests of thyroid function and of glucose metabolism. Baranski and Czerski (5) report research along these lines.

The question of pumping of biomacromolecules can be examined experimentally, or indirectly, as indicated above, by searching for biomedical evidence in animals or in in-vitro chemical reaction experiments. More direct evidence can be obtained via spectroscopic measurements and molecular models as pursued by Prohofsky and his colleagues (6, 7). This research group has produced evidence of stimulation of homopolymer DNA and RNA molecules in electromagnetic fields by gigahertz radiofrequency radiation. The biomedical relevance of this work needs further research. Of paticular interest is the question of whether molecular stimulation can occur at field frequencies of less than 1 GHz.

To summarize Part I of this report, the model tissue presented here suggests the possibility of molecular stimulation, or pumping, by electromagnetic radiation. Such a phenomenon could be expected to lead to changed chemical reactivity, and research along these lines, found in the literature, is mentioned. The possibility of linking molecular stimulation with biomedical effects is broached. The concept of molecular stimulation or pumping by electromagnetic radiation requires more and deeper investigation both from the point of view of biophysics and from the vantage point of biomedical effects. The present picture is far from complete.

As a small step toward an improved understanding of molecular stimulation, a more detailed model of macromolecular responses in an electromagnetic field is presented in the next section of this report.

PART II: ON MACROMOLECULAR MOTION IN AN ELECTROMAGNETIC FIELD

A very simple one-dimensional chain molecule is used to illustrate basic concepts and principles. The model molecule consists of n components connected by n-1 forces having linear spring properties. The coordinates for the components are $x_0, x_1, \ldots\ldots, x_{n-1}$; each component has mass m, and each connecting force has force constant k. Each component carries electric charge $q_0, q_1, \ldots\ldots, q_{n-1}$. Figure 5 presents the model schematically. The mathematical treatment presented in this section is an adaptation and extension of the analysis provided by Muzushima (8). The model is a simple application of lattice theory (9, 10). The setting is nonquantum mechanical or classical in approach.

The equations of motion for the model molecule are:

$$\begin{aligned}
m\ddot{x}_0 &= -k(x_0 - x_1) + q_0 E \sin \omega t \\
m\ddot{x}_1 &= k(x_0 - x_1) - k(x_1 - x_2) + q_1 E \sin \omega t \\
m\ddot{x}_2 &= k(x_1 - x_2) - k(x_2 - x_3) + q_2 E \sin \omega t \\
&\quad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
m\ddot{x}_{n-1} &= k(x_{n-2} - x_{n-1}) + q_{n-1} E \sin \omega t
\end{aligned} \tag{10}$$

where E is the peak electric-field strength.

When divided by m and rearranged, these equations of motion become:

$$\begin{aligned}
\ddot{x}_0 &= -1x_0 + 1x_1 + \varepsilon_0 \sin \omega t \\
\ddot{x}_1 &= 1x_0 - 2x_1 + 1x_2 + \varepsilon_1 \sin \omega t \\
\ddot{x}_2 &= 1x_1 - 2x_2 + 1x_3 + \varepsilon_2 \sin \omega t \\
&\quad \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
\ddot{x}_{n-1} &= 1x_{n-2} - 1_{n-1} + \varepsilon_{n-1} \sin \omega t
\end{aligned} \tag{11}$$

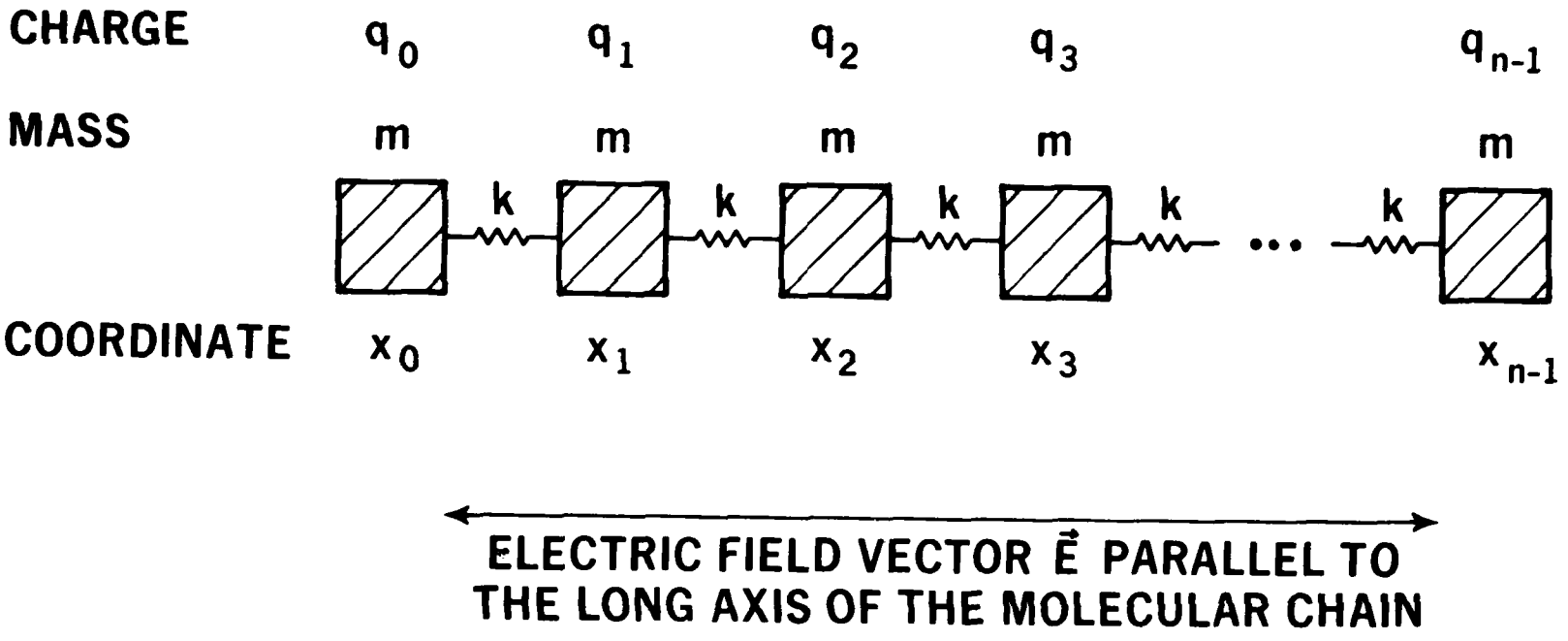

Figure 5. A model macromolecule.

where $l = k/m$ and $\varepsilon_i = q_i E/m$.

Equations 11 can be written in matrix form as:

$$\ddot{\underline{X}} = -L\underline{X} + \underline{\varepsilon} \sin \omega t \qquad (12)$$

where

$$\underline{X} = \begin{bmatrix} x_0 \\ x_1 \\ x_2 \\ \cdot \\ \cdot \\ \cdot \\ x_{n-1} \end{bmatrix} \qquad \underline{\varepsilon} = \begin{bmatrix} \varepsilon_0 \\ \varepsilon_1 \\ \varepsilon_2 \\ \cdot \\ \cdot \\ \cdot \\ \varepsilon_{n-1} \end{bmatrix}$$

and

$$L = \begin{bmatrix} 1 & -1 & 0 & 0 & 0 & & \\ -1 & 21 & -1 & 0 & 0 & & \\ 0 & -1 & 21 & -1 & 0 & & \\ 0 & 0 & -1 & 21 & -1 & & \\ & & & & \cdot & & \\ & & & & & \cdot & \\ & & & & & -1 & 1 \end{bmatrix}$$

Now, a matrix A is sought such that

$$A^T A = I \qquad A^T L A = R$$

where A^T is the transpose of the matrix A, I is the identity matrix, and R is a diagonal matrix. For the problem under consideration here, such a matrix A can be found. Specifically, if

$$A = \begin{bmatrix} a_{00} & a_{01} & a_{02} & \cdots & a_{0,\,n-1} \\ a_{10} & a_{11} & a_{12} & \cdots & a_{1,\,n-1} \\ a_{20} & a_{21} & a_{22} & \cdots & a_{2,\,n-1} \\ \vdots & \vdots & \vdots & & \vdots \\ a_{n-1,\,0} & a_{n-1,\,1} & a_{n-1,\,2} & \cdots & a_{n-1,\,n-1} \end{bmatrix}$$

then

$$a_{ij} = \left(\frac{2}{n+1} \right)^{1/2} \cos \left[(j+1/2)\, i\pi/n \right] \tag{13}$$

and writing R as,

$$R = \begin{bmatrix} r_0 & 0 & 0 & 0 & & \\ 0 & r_1 & 0 & 0 & & \\ 0 & 0 & r_2 & 0 & & \\ & & & \ddots & & \\ & & & & & r_{n-1} \end{bmatrix}$$

the r_i are given by:

$$r_i = 2l\left[1 - \cos \left(\frac{i\pi}{n} \right)\right] \tag{14}$$

Equations 13 and 14 are shown in Mizushima (8).

Define $\lambda_i^2 = r_i$. The terms λ_i will be very important as they represent natural frequencies associated with the molecular motion, as shall be seen below.

Define new molecular coordinates $\underline{\xi}$, using the matrix A, as

$$\underline{X} = A\underline{\xi}$$

Then equation 12 becomes

$$A\ddot{\underline{\xi}} = -LA\underline{\xi} + \underline{\epsilon} \sin \omega t$$

By multiplying this equation from the left by A^T, the following important equation is obtained:

$$\ddot{\underline{\xi}} = -A^T L A\underline{\xi} + A^T\underline{\epsilon} \sin \omega t$$

or

$$\ddot{\underline{\xi}} = -R\underline{\xi} + A^T\underline{\epsilon} \sin \omega t \tag{15}$$

Written in component form, equation 15 becomes the set of equations

$$\ddot{\xi}_0 = -\lambda_0^2 \xi_0 + \left[\sum_{j=0}^{n-1} a_{0j}^T \varepsilon_j\right] \sin \omega t$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$\ddot{\xi}_i = -\lambda_i^2 \xi_i + \left[\sum_{j=0}^{n-1} a_{ij}^T \varepsilon_j\right] \sin \omega t \qquad (16)$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$\ddot{\xi}_{n-1} = -\lambda_{n-1}^2 \xi_{n-1} + \left[\sum_{j=0}^{n-1} a_{n-1,j}^T \varepsilon_j\right] \sin \omega t$$

where a_{ij}^T is the i, jth element in A^T.

Comparing the above set of equations with the set given before as equation 11, we see that in the above set each equation involves just a single ξ_i; while with equation 11, each equation involves more than one x_i. The set of equations labelled equation 16 thus defines, in a sense, independent components of motion. In fact, the ξ_i's are called normal or collective components, and the modes of motion they describe are called normal modes.

Looking again at equation 16, we see n independent oscillators. The solution can be found by elementary methods. Specifically, when $\lambda_i \neq \omega$:

$$\xi_i(t) = \xi_i(0)\cos \lambda_i t + [\dot{\xi}_i(0)/\lambda_i] \sin \lambda_i t$$

$$+ \left[\sum_{j=0}^{n-1} a_{ij}^T \varepsilon_j\right]\left[\frac{\omega}{\lambda_i^2-\omega^2}\right]\left[\frac{\sin \omega t}{\omega} - \frac{\sin \lambda_i t}{\lambda_i}\right] \qquad (17)$$

and, when $\lambda_i = \omega$

$$\xi_i(t) = \xi_i(0)\cos\,\omega t + [\dot{\xi}_i(0)/\omega]\sin\,\omega t$$

$$+ \Big[\sum_{j=0}^{n-1} a_{ij}^T\,\varepsilon_j\Big]\Big[\frac{1}{2\omega^2}\Big][\sin\,\omega t - \omega t\cos\,\omega t] \qquad (18)$$

The values $\xi_i(0)$ and $\dot{\xi}_i(0)$ are the coordinate position and velocity, respectively, at time t = 0 which is considered to be the beginning of the macromolecular exposure to the electric field. These values reflect the thermal state of the molecule just prior to imposition of the field. Also, note that λ_i defines the intrinsic frequency response of the ith oscillator.

The molecular perturbation due to the electric field is symbolized by $\xi_i^T(t)$, and these perturbations are given by equation 19 and equation 20 below. For $\lambda_i \neq \omega$

$$\xi_i^E(t) = \Big[\sum_{j=0}^{n-1} a_{ij}^T\,\varepsilon_j\Big]\Big[\frac{\omega}{\lambda_i^2-\omega^2}\Big]\Big[\frac{\sin\,\omega t}{\omega} - \frac{\sin\,\lambda_i t}{\lambda_i}\Big] \qquad (19)$$

and for $\lambda_i = \omega$

$$\xi_i^E(t) = \Big[\sum_{j=0}^{n-1} a_{ij}^T\,\varepsilon_j\Big]\Big[\frac{1}{2\omega^2}\Big][\sin\,\omega t - \omega t\cos\,\omega t] \qquad (20)$$

Note at this point that for $\lambda_i \neq \omega$, the perturbation $\xi_i^E(t)$ remains bounded; but for $\lambda_i = \omega$, $\xi_i^E(t)$ grows linearly with time. It is instructive to look at the energy of the molecule as a function of the electromagnetic perturbation. The kinetic energy of the molecule is

$$\text{K.E.} = \frac{1}{2}\,m\,\underline{\dot{X}}^T\underline{\dot{X}} = \frac{1}{2}\,m\,\underline{\dot{\xi}}^T\underline{\dot{\xi}}$$

while the potential energy of the molecule is

$$\text{P.E.} = \frac{1}{2}\,m\,\underline{X}^T L\underline{X} = \frac{1}{2}\,m\,\underline{\xi}^T R\underline{\xi}$$

Using the above facts, we state the molecular energy due to electromagnetic perturbation of the ξ_i coordinate as

$$W_i = \frac{1}{2} m \dot{\xi}_i^2 + \frac{1}{2} m \lambda_i^2 \xi_i^2$$

Using this last equation and equations 19 and 20, we find that for $\lambda_i \neq \omega$

$$W_i = \frac{1}{2} m [\omega^2/(\lambda_i^2 - \omega^2)^2] [\sum_{j=0}^{n-1} a_{ij}^T \epsilon_j]^2 \{1 + \cos^2 \omega t + (\lambda_i^2/\omega^2)\sin^2 \omega t - 2 \cos \omega t \cos \lambda_i t - 2(\lambda_i/\omega)\sin \omega t \sin \lambda_i t\} \quad (21)$$

and for $\lambda_i = \omega$

$$W_i = (m/8\omega^2)[\sum_{j=0}^{n-1} a_{ij}^T \epsilon_j]^2 \{1 + \omega^2 t^2\} \quad (22)$$

These last two equations are of particular interest. When the stimulating frequency ω is not equal to a natural frequency of the molecule λ_i, the absorbed energy is a finite quantity, as indicated by equation 21. This absorbed energy can be compared with the thermal energy in an individual normal mode, which is kT (k = Boltzmann constant, T = temperature in °K) by the equivalence principle (11). When the stimulating frequency ω equals a natural mode frequency of the molecule (the resonance case), the molecule gains energy quadradically with time, as seen in equation 22. If, at resonance, the molecule cannot adequately dissipate absorbed energy, molecular disruption would be expected.

Based upon equations 21 and 22, but particularly equation 22 with the resonance response, developing a fuller understanding of molecular dynamics in a radiofrequency field is clearly important. Two questions are immediate. (1) What are the natural frequencies of biomacromolecules in tissue? (2) What energy dissipative mechanisms are available to biomacromolecules in tissue? These two questions will now be addressed in the context of the simple linear chain model already under discussion.

BIOMOLECULAR NATURAL VIBRATIONAL FREQUENCIES

Regarding the natural frequencies of biomacromolecules in tissue, equation 14 can be used to provide a first approximation. Using k = 3 millidynes per Angstrom, m = 200 gram molecular weight, and N = 2000, the lowest ten natural frequencies of the chain model are given in Table 6. The value of k (3 millidynes per Angstrom) reflects the type of force constant one can find in a carbon-carbon bond. The m and N values employed in constructing Table 6 provide a macromolecule with gram molecular weight equal to 400,000.

TABLE 6. THE LOWEST TEN NATURAL FREQUENCIES IN A MODEL MACROMOLECULE

GHz
0.000
7.512
15.025
22.537
30.050
37.562
45.075
52.587
60.100
67.612

In Table 6 the lowest frequency, zero, corresponds to direct acceleration or translation of the entire molecule by the electromagnetic field. The next lowest frequency is an internal vibratory mode. This mode and several others are in the low gigahertz range. If the model were made longer and/or heavier, natural vibratory modes could be found in the 100 to 900 MHz range. Such molecules would be quite large linear structures, however. More complete calculations and spectroscopic data are needed to determine the extent to which vibratory resonances occur below 1 GHz. However, a brief glance at most spectroscopy texts will rapidly convince the reader that rotational modes are commonly found below 1 GHz. Again, future research will determine the occurrence and biomedical meaning of these modes.

AVAILABLE DISSIPATIVE MECHANISMS

Two dissipative mechanisms come immediately to mind for consideration: radiation of energy, and loss of energy via collisional events.

The molecular charges q_i, when they move, will lose energy by setting up a radiation field. A damping force, F_i, is associated with this radiation as the moving charge interacts with its own field. This force is given by

$$F_i = (q_i^2/8\pi\varepsilon_0 c^2 r_0^i)\ddot{x}_i - (q_i^2/6\pi\varepsilon_0 c^3)\dddot{x}_i + \cdots \quad (23)$$

In this equation, c is the speed of light, ε_0 is the capacitivity of the vacuum, and r_0^i is the radius of the ith-charged particle. Higher order terms in this force equation are neglected for they converge towards zero as r_0^i approaches zero (8). Equation 23 will be incorporated into equation 10.

Collisional events will exert a damping force on molecular motion also. In general, the collisional damping on the ith molecular component will be $\beta_i\dot{x}_i$ where β_i is a coefficient of friction.

With the above considerations, equation 10 becomes:

$$\begin{aligned}
m\ddot{x}_0 &= -k(x_0 - x_1) - a_0 q_0^2 \ddot{x}_0 + bq_0^2 \dddot{x}_0 - \beta_0 \dot{x}_0 + q_0 E \sin\omega t \\
m\ddot{x}_1 &= k(x_0 - x_1) - k(x_1 - x_2) - a_1 q_1^2 \ddot{x}_1 + bq_1^2 \dddot{x}_1 - \beta_1 \dot{x}_1 + q_1 E \sin\omega t \\
m\ddot{x}_2 &= k(x_1 - x_2) - k(x_2 - x_3) - a_2 q_2^2 \ddot{x}_2 + bq_2^2 \dddot{x}_2 - \beta_2 \dot{x}_2 + q_2 E \sin\omega t \quad (24) \\
&\ \ \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\
m\ddot{x}_{n-1} &= k(x_{n-2} - x_{n-1}) - a_{n-1} q_{n-1}^2 \ddot{x}_{n-1} + bq_{n-1}^2 \dddot{x}_{n-1} - \beta_{n-1} \dot{x}_{n-1} + q_{n-1} E \sin\omega t
\end{aligned}$$

where $a_i = 1/(8\pi\xi_0 c^2 r_0^i)$ and $b = 1/(6\pi\xi_0 c^3)$. Rearranging, we obtain the following:

$$-bq_0^2\dddot{x}_0 + (m+a_0q_0^2)\ddot{x}_0 + \beta_0\dot{x}_0 = -kx_0 + kx_1 + q_0E\sin\omega t$$

$$-bq_1^2\dddot{x}_1 + (m+a_1q_1^2)\ddot{x}_1 + \beta_1\dot{x}_1 = kx_0 - 2kx_1 + kx_2 + q_1E\sin\omega t$$

$$-bq_2^2\dddot{x}_2 + (m+a_2q_2^2)\ddot{x}_2 + \beta_2\dot{x}_2 = kx_1 - 2kx_2 + kx_3 + q_2E\sin\omega t \quad (25)$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$-bq_{n-1}^2\dddot{x}_{n-1} + (m+a_{n-1}q_{n-1}^2)\ddot{x}_{n-1} + \beta_{n-1}\dot{x}_{n-1} = kx_{n-2} - kx_{n-1} + q_{n-1}E\sin\omega t$$

Let $r_0^0 = r_0^1 = r_0^2 = \ldots = r_0^{n-1} = r_0$, so that $a_0 = a_1 = a_2 = \ldots = a_{n-1} = a$, and let $q_0^2 = q_1^2 = q_2^2 = \ldots = q_{n-1}^2 = q^2$, $\beta_0 = \beta_1 = \beta_2 = \ldots = \beta_{n-1} = \beta$, $\hat{m} = m + aq^2$, $\tau = -bq^2/m$, $\hat{l} = k/\hat{m}$, $\hat{\beta} = \beta/\hat{m}$, and $\hat{\varepsilon}_i = q_iE/\hat{m}$. Then equation 25 becomes:

$$\hat{\tau}\dddot{x}_0 + \ddot{x}_0 + \hat{\beta}\dot{x}_0 = -\hat{l}x_0 + \hat{l}x_1 + \hat{\varepsilon}_0\sin\omega t$$

$$\hat{\tau}\dddot{x}_1 + \ddot{x}_1 + \hat{\beta}\dot{x}_1 = \hat{l}x_0 - 2\hat{l}x_1 + \hat{l}x_2 + \hat{\varepsilon}_1\sin\omega t$$

$$\hat{\tau}\dddot{x}_2 + \ddot{x}_2 + \hat{\beta}\dot{x}_2 = \hat{l}x_1 - 2\hat{l}x_2 + \hat{l}x_3 + \hat{\varepsilon}_2\sin\omega t \quad (26)$$

$$\vdots \qquad \vdots \qquad \vdots$$

$$\hat{\tau}\dddot{x}_{n-1} + \ddot{x}_{n-1} + \hat{\beta}\dot{x}_{n-1} = \hat{l}x_{n-2} - \hat{l}x_{n-1} + \hat{\varepsilon}_{n-1}\sin\omega t$$

In matrix form equation 26 is:

$$\hat{\tau}\dddot{\underline{X}} + \ddot{\underline{X}} + \hat{\beta}\dot{\underline{X}} = -\hat{L}\underline{X} + \hat{\varepsilon}\sin\omega t$$

Again using $\underline{X} = A\underline{\xi}$, we obtain

$$\hat{\tau}\dddot{\underline{\xi}} + \ddot{\underline{\xi}} + \hat{\beta}\dot{\underline{\xi}} = -\hat{R}\underline{\xi} + A^T\underline{\hat{\varepsilon}} \sin \omega t \tag{27}$$

where $\hat{R}$ is a diagonal matrix with entries

$$\hat{r}_i = 2\hat{I}\left[1 - \cos\left(\frac{i\pi}{n}\right)\right] = \hat{\lambda}_i^2 \tag{28}$$

The ith component of the matrix equation, equation 27, is

$$\hat{\tau}\dddot{\xi}_i + \ddot{\xi}_i + \hat{\beta}\dot{\xi}_i + \hat{\lambda}_i^2 \xi_i = \left[\sum_{j=0}^{n-1} a_{ij}^T \hat{\varepsilon}_j\right] \sin \omega t$$

Solving, we find that for $\hat{\lambda}_i \neq \omega$, the molecular perturbation due to the electric field of the ith coordinate is:

$$\xi_i^E(t) = \sum_{j=0}^{n-1} a_{ij}^T \hat{\varepsilon}_j \left[\frac{(\hat{\lambda}_i^2 - \omega^2) \sin \omega t - (\hat{\beta}\omega - \hat{\tau}\omega^3) \cos \omega t}{(\hat{\lambda}_i^2 - \omega^2)^2 + (\hat{\beta}\omega - \hat{\tau}\omega^3)^2}\right] \tag{29}$$

When $\hat{\lambda}_i = \omega$ (i.e., at resonance)

$$\xi_i^E = -\left[\sum_{j=0}^{n-1} a_{ij}^T \hat{\varepsilon}_j\right] \frac{\cos \omega t}{(\hat{\beta}\omega - \hat{\tau}\omega^3)} \tag{30}$$

and

$$\dot{\xi}_i^E = \left[\sum_{j=0}^{n-1} a_{ij}^T \hat{\varepsilon}_j\right] \frac{\omega \sin \omega t}{(\hat{\beta}\omega - \hat{\tau}\omega^3)} \tag{31}$$

Using

$$W_i = (1/2)m\dot{\xi}_i^2 + (1/2)m\hat{\lambda}_i^2 \xi_i^2$$

we find that

$$W_i = (1/2)\, m \left[\sum_{j=0}^{n-1} a_{ij}^T \hat{\varepsilon}_j\right]^2 \Big/ (\hat{\beta} - \hat{\tau}\omega^2)^2 \tag{32}$$

From this last equation we see that molecular energy remains finite at resonance when we consider the effect of dissipative mechanisms (remember that $\hat{\tau}$ is a negative number).

With equations 28 and 32 in hand, we can appropriately reconsider the 400,000 molecular weight macromolecule studied earlier. Recall that this macromolecule was defined by the following parameters: k = 3 millidynes per Angstrom, m = 200 gram molecular weight, N = 2000. For the present analysis, we will consider charges symmetrically placed on the molecule. Specifically, let us assume that q_0 through q_{665} equal 0.0015015 times the charge on one electron ($-1.6021917 \times 10^{-19}$ Coulomb), q_{666} through q_{1333} equal 0.0015015 times the charge on one positron, and q_{1334} through q_{1999} equal 0.0015015 times the charge on one electron. This charge distribution provides one electron charge spread over the left and right outer one-third parts of the chain model molecule, and provides one positron charge over the central one-third portion of the molecule.

For r_0, we use value 2.817939×10^{-15} m, a calculated electron radius (8). Of course, $\varepsilon_0 = 8.85419 \times 10^{-12}$ Farads/m, $c = 2.9979 \times 10^8$ m/second. The only term left undecided is the friction coefficient β. In Appendix C we see that

$$\beta = m/2\tau \tag{33}$$

where m is the mass of the macromolecular component and τ is the time constant of the molecule relative to energy dissipation by collisional mechanisms.

Working first with equation 28, we see immediately that, since $\hat{m}$ is only very slightly larger than m, the molecular natural frequencies with dissipation, $\hat{\lambda}_i$, are essentially unchanged from the natural frequencies λ_i without damping. Working at the lowest frequency of 7.512 GHz and using equation 32, we calculate the data in Figure 6. Appendix D provides the computer program used to accomplish these calculations.

Studying Figure 6, we again see a phenomenon that was first noted in Part I of this report. Namely, when the molecular mode is shielded from collisional exchanges, the electromagnetic field is able to significantly excite the mode. Note specifically that at higher time constants, mode energies considerably above kT are seen. Further analysis and experimentation are needed to determine whether any such high time constants actually

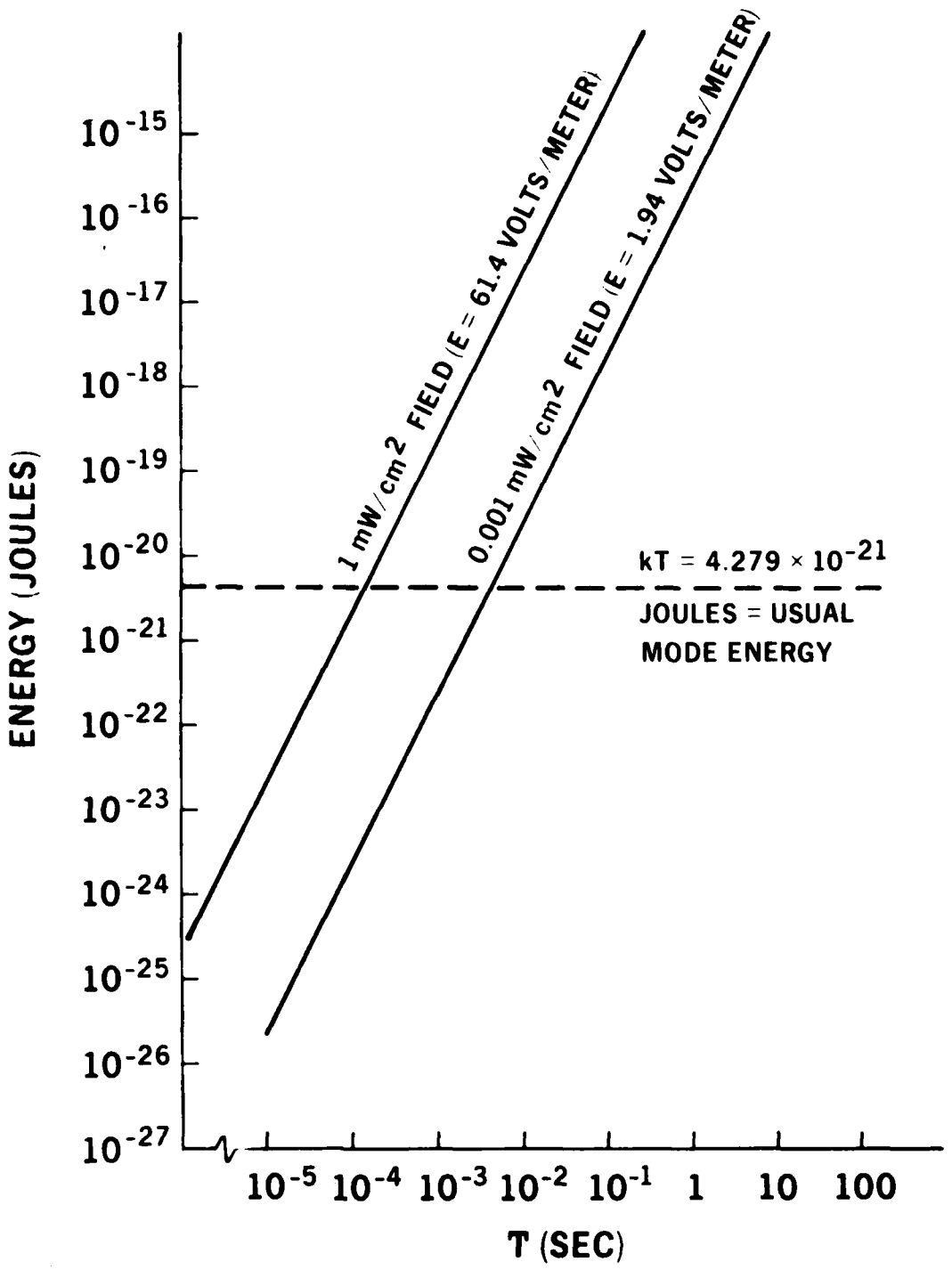

Figure 6. Normal mode energy vs. RFR exposure and molecule relaxation time T.

obtain in living tissue. As discussed in Part I, molecular stimulation or pumping could be detected as changed chemical reactivity or by spectroscopic measurements.

Figure 7 presents a schematic of molecular structure which might evidence modes of motion that are shielded from collisional exchanges but are susceptible to electromagnetic-field stimulation. The inner molecular moieties are proposed as the potentially susceptible moieties. In Figure 8 the molecular structure introduced in Figure 7 is shown interacting with another compound to form a more complex entity. This complex entity is intended to represent an antigen-antibody combination or another similar receptor-site interaction. Again, the inner molecular moieties would be shielded from collisional energy exchanges but could be potentially susceptible to perturbation by electromagnetic fields. This concept that receptor-site mechanisms could be perturbed by electromagnetic radiation leads to the conjecture that biological events that involve coding and decoding may be susceptible to radiofrequency radiation. For example, DNA-RNA transcription events could be vulnerable, as could be antigen-antibody immunological responses. Autoimmune antibody has been noted in animals chronically irradiated with radiofrequency radiation. This leads us to consider whether radiofrequency radiation might not be implicated in the genesis of collagen diseases such as lupus erythematosus or scleroderma (12).

PART III: DISCUSSION

In Part I of this report an elementary statistical physics model of tissue was presented. This model suggested that molecular transitions which were shielded from collisional energy exchanges could be stimulated by electromagnetic radiation. Part II of this report presented a simple model linear chain macromolecule. This macromolecule exhibited natural frequencies in the low gigahertz range. Once again it was seen that if a molecular mode were shielded from collisional energy exchanges, electromagnetic stimulation could obtain. Biomedical consequences of macromolecular electromagnetic stimulation would be effects following changed macromolecular chemical reactivity, as stimulation of molecular modes of motion could potentially change the ability of the molecule to engage in specific chemical reactions. The pivotal point now appears to be the question of how a macromolecule

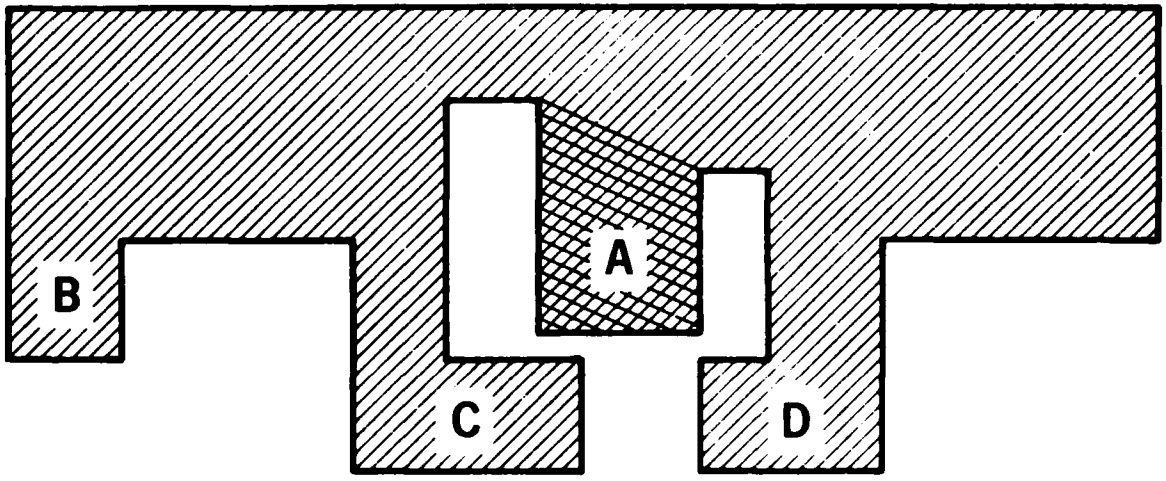

Figure 7. Schematic of a molecular structure which might evidence modes of motion which are shielded from collisional exchanges but susceptible to electromagnetic field stimulation. The inner moiety A is potentially susceptible.

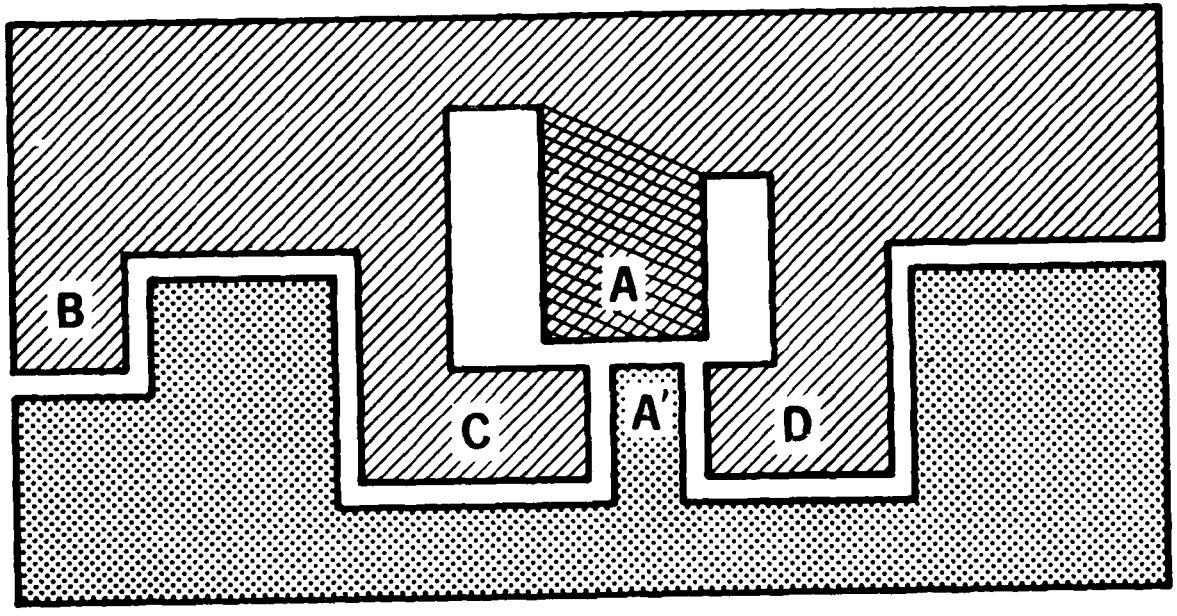

Figure 8. Schematic of a molecular combination. Moieties A, A', C and D could be vulnerable to electromagnetic radiation.

dissipates energy absorbed from an electromagnetic field. A central question concerns the collisional mechanisms available to a macromolecule in living tissue. This question can be examined by studying chemical reactions in tissue or tissue-equivalent material. Also, more directly, electromagnetic absorption data obtained from macromolecules in a tissue milieu will help elucidate dissipation mechanisms.

In this report's treatment of a biomacromolecule imbedded in a medium, electromagnetic radiation that will be incident upon the molecule from adjacent macromolecules as well as from external sources is not included. This internal radiation exchange needs and warrants further investigation.

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APPENDIX A

DERIVATION OF EQUATIONS 4 AND 5

Molecules of two types, #1 and #2, are treated. Type #1 molecules can occupy energy levels U_{11}, U_{12}, U_{13}, ..., U_{1L}, and type #2 molecules can occupy energy levels U_{21}, U_{22}, U_{23}, ..., U_{2M}. The symbol x_{ij} represents the number of molecules of type i in energy level j. To determine the most likely values n_{ij}, of the x_{ij}'s, the probability of the different possible system configurations is maximized under the constraints of (a) constant total molecules of each type, and (b) constant total system energy. Thus,

$$P(x_{11}, \ldots, x_{1L}; x_{21}, \ldots, x_{2M}) =$$

$$\left\{\frac{N_1!}{x_{11}!\, x_{12}! \cdots x_{1L}!}\, p_{11}^{x_{11}} \quad p_{12}^{x_{12}} \quad \cdots \quad p_{1L}^{x_{1L}}\right\} \times$$

$$\left\{\frac{N_2!}{x_{21}!\, x_{22}! \cdots x_{2M}!}\, p_{21}^{x_{21}} \quad p_{22}^{x_{22}} \quad \cdots \quad p_{2M}^{x_{2M}}\right\} \qquad \text{(A1)}$$

is maximized with constraints

$$\sum_{j=1}^{L} x_{1j} = N_1 = \text{total number of type \#1 molecules}$$

$$\sum_{j=1}^{M} x_{2j} = N_2 = \text{total number of type \#2 molecules}$$

$$\sum_{j=1}^{L} x_{1j}U_{1j} + \sum_{j=1}^{M} x_{2j}U_{2j} = U = \text{total system (mixture) energy}$$

The function $P(x_{11}, \ldots; x_{1L}, x_{21}, \ldots, x_{2M})$ is the product of two multinomial distributions where the constants p_{ij} are the probabilities that a molecule of type i can enter its jth energy level (1).

The maximization is achieved by working with the natural logarithm of P, using Lagrange multipliers a, b, and c, and solving the following equation (2):

$$d\ln P + adN_1 + bdN_2 + cdU = 0$$

Note that

$$dS = kd\ln P$$

where S is system entropy and k is the Boltzmann constant; and recall the thermodynamic equation

$$TdS + \mu_1 dN_1 + \mu_2 dN_2 - dU = 0$$

to determine immediately that (3)

$$c = -(kT)^{-1}$$

Using Stirling's formula ($\ln R! \approx R\ln R - R$),

$$d\ln P \approx \sum_{j=1}^{L} (\ln p_{1j} - \ln x_{1j})\, dx_{1j} + \sum_{j=1}^{M} (\ln p_{2j} - \ln x_{2j}) dx_{2j} \qquad (A2)$$

whence

$$d\ln P + adN_1 + bdN_2 + cdU \approx$$

$$\sum_{j=1}^{L} (\ln p_{1j} - \ln x_{1j} + a + cU_{1j}) dx_{1j}$$

$$+ \sum_{j=1}^{M} (\ln p_{2j} - \ln x_{2j} + b + cU_{2j}) dx_{2j}$$

and, for occupancy numbers x_{ij}, such that Stirling's formula is accurate, $P(x_{11}, \ldots, x_{12}, x_{21}, \ldots, x_{2m})$ is maximized by $x_{1j}=n_{1j}$ and $x_{2j}=n_{2j}$, where

$$n_{1j} = p_{1j} e^{+a} e^{-U_{1j}/kT}$$

and

$$n_{2j} = p_{2j} e^{+b} e^{-U_{2j}/kT}$$

Using the relations

$$\sum_{j=1}^{L} x_{1j} = N_1$$

$$\sum_{j=1}^{M} x_{2j} = N_2$$

the constants a and b can be found, providing equations 4 and 5 of the text. Differentiating equation A2 confirms that the n_{ij}'s maximize P.

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APPENDIX B

BASIC LANGUAGE COMPUTER PROGRAM FOR CALCULATING THE DATA FOUND IN TABLES 2 THROUGH 5 AND IN FIGURES 2 THROUGH 4

```
10 REM THE TITLE OF THIS PROGRAM IS EQUIL
20 DIM P1(2), P2(2), U1(2), U2(2)
30 DIM A1(2), A2(2)
40 P1(1)=0.70
50 P1(2)=0.30
60 P2(1)=0.9999
70 P2(2)=0.0001
80 N1=1.4E11
90 N2=1.0E6
100 T=310
110 V=500E6
120 H=6.6252E-34
130 K=1.3804E-23
140 U1(1)=1.0*K*310
150 U1(2)=2.0*K*310
160 U2(1)=1.5*K*310
170 U2(2)=1.5*K*310 + H*V
180 Z1=P1(1)*EXP(-U1(1)/(K*T)) + P1(2)*EXP(-U1(2)/(K*T))
190 Z2=P2(1)*EXP(-U2(1)/(K*T)) + P2(2)*EXP(-U2(2)/(K*T))
200 FOR I=1TO 2
210 A1(I)=P1(I)*N1*EXP(-U1(I)/(K*T))/Z1
220 A2(I)=P2(I)*N2*EXP(-U2(I)/(K*T))/Z2
230 NEXT I
240 E=A1(1)*U1(1)+A1(2)*U1(2)+A2(1)*U2(1)+A2(2)*U2(2)
250 PRINT
260 PRINT "TEMP", T
270 PRINT
280 PRINT "N1(1)",A1(1)
290 PRINT "N1(2)",A1(2)
300 PRINT "N2(1)",A2(1)
```

```
310 PRINT "N2(2)",A2(2)
320 PRINT
330 PRINT "ENERGY", E
340 DIM C2(2)
350 B=750
360 C2(1)=0.0375
370 C2(2)=C2(1)*(A2(1)/A2(2))
380 PRINT
390 PRINT "C2(1)",C2(1)
400 PRINT "C2(2)",C2(2)
410 I=.001
420 D=(B*I*(A2(1)-A2(2)))/(2*B*I+C2(1)+C2(2))
430 PRINT
440 PRINT "I",I
450 PRINT "DELTA",D
460 A2(1)=A2(1)-D
470 A2(2)=A2(2)+D
480 PRINT
490 PRINT "NEW N2(1)",A2(1)
500 PRINT "NEW N2(2)",A2(2)
510 E=A1(1)*U1(1)+A1(2)*U1(2)+A2(1)*U2(1)+A2(2)*U2(2)
520 PRINT
530 PRINT "NEW E",E
540 END
```

APPENDIX C

DERIVATION OF EQUATION 33

It is well known that drag forces on a surface are proportional to the velocity gradient perpendicular to the surface (1). Thus a term $\beta_i \dot{x}_i$ is inserted in equation 24. If $\beta_i \dot{x}_i$ is the drag force, then $\beta_i \dot{x}_i^2$ must be the rate at which energy is lost via these forces. That is:

$$\frac{dE}{dt} = -\beta_i \dot{x}_i^2 \qquad \text{(C1)}$$

Drag forces are the result of collisional events between the macromolecule and its solvent. In colliding with the macromolecule, solvent molecules can change the partitioning of energy in the macromolecule. Specifically, collisions can change the energy of vibration or the energy associated with electron motion in the macromolecule. Thus E may be written as:

$$E = E_v + E_e$$

where E_v is the energy of vibrational motion and E_e is the electron energy. Equation C1 can be written

$$\frac{dE}{dt} = -\frac{2\beta_i}{m} E_{kv} = -\frac{E_{kv}}{T}$$

where E_{kv} is the instantaneous kinetic energy of vibration and T is the desired time constant.

REFERENCE

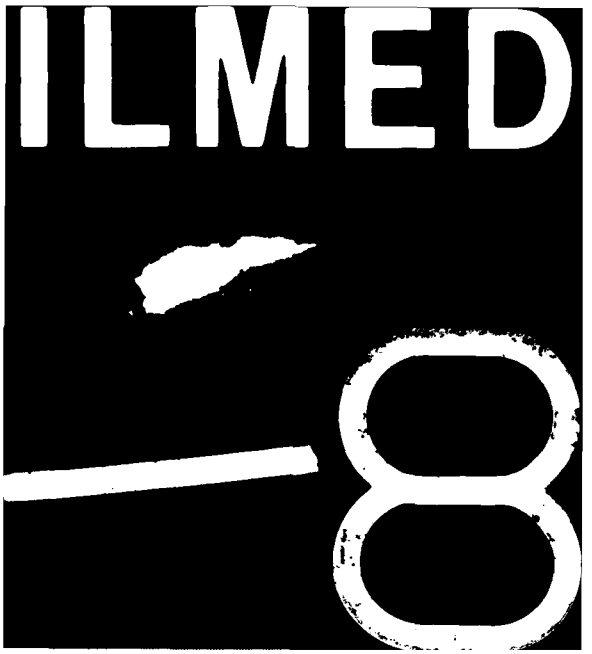
1. Reimann, A. L. Physics. New York: Barnes and Noble, Inc., 1971.

APPENDIX D

BASIC LANGUAGE COMPUTER PROGRAM USED TO CALCULATE DATA IN FIGURE 6

```
10 REM CALCULATION OF W
20 SELECT R
30 REM CALCULATE SUM OVER J OF A(JI)*Q(J)
40 I=1
50 N=2000
60 S1=0.0
70 Q=1.6021917E-19
80 FOR J=0 TO 665
90 FO=-0.0015015
100 Z=COS((I+0.5)*J*#PI/N)*FO*Q
110 S1=S1+Z
120 NEXT J
130 FOR J=666 TO 1333
140 FO=0.0015015
150 Z=COS((I+0.5)*J*#PI/N)*FO*Q
160 S1=S1+Z
170 NEXT J
180 FOR J=1334 TO 1999
190 FO=-0.0015015
200 Z=COS((I+0.5)*J*#PI/N)*FO*Q
210 S1=S1+Z
220 NEXT J
230 PRINT "SUM(A(JI)*Q(J))",S1
240 M=200
250 M=M/6.02E26
260 REM B IS FRICTION COEFFICIENT
270 INPUT "T",T
280 B=0.5*M/T
290 EO=8.85419E-12
300 C=2.9979E8
```

```
310 R0=2.817939E-15
320 A0=8*#PI*E0*C^2*R0
330 A0=1/A0
340 B0=6*#PI*E0*C^3
350 B0=1/B0
360 E=61.40
370 L=2*#PI*7.512E6
380 M1=M+A0*(F0*Q)^2
390 B1=B/M1
400 T1=-(B0*(F0*Q)^2)/M1
410 D=1/(B1-T1*L^2)
420 S2=SQR(2/(N-1))*S1
430 S2=(E/M1)*S2
440 W=0.5*M*(D*S2)^2
450 PRINT "T",T
460 PRINT "W",W
470 END
```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